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Oral contraception and health

Long term study of mortality shows no overall effect in a developed country

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Oral contraceptives have been studied more intensively than any other medication in history. Yet the recent brouhaha about third generation oral contraceptives and venous thromboembolism is only the latest in a series of "pill scares" over more than three decades. For some mysterious reason these periodic crises have been a particular feature of Britain; during the 1980s, for example, false alarms about major effects on breast cancer risk created greater consternation in Britain than elsewhere. While the British media have often produced more heat than light, scientists in Britain have contributed more than their share of evidence about the safety of oral contraceptives. One project that has become a landmark of epidemiology is the Royal College of General Practitioners' oral contraception study, and this week sees another publication from the study (p 96).[1]

In 1968 Dr Clifford Kay and his colleagues persuaded 1400 general practitioners to enrol 46 000 women (half of whom were using oral contraceptives at the time) into a follow up study. Meticulous observations over many years have produced important information about many health outcomes.[2,3] In this issue Beral et al report on mortality experience over 25 years, during which 1599 deaths were recorded.[1] Over the entire period oral contraception did not increase or decrease total mortality (relative risk = 1.0, 95% confidence interval 0.9 to 1.1). As expected from other studies, women who used oral contraceptives had a lower death rate from ovarian cancer and higher mortality from circulatory diseases (including stroke) and cervical cancer. These features were seen mainly while women were using the pill and in the 10 years afterwards. Most of the preparations used by women in this study were combined oral contraceptives containing 50μg of oestrogen.

A balance sheet of benefits and risks based on one cohort study is intriguing and valuable, but this analysis also shows the limitations of the prospective approach.[4] Despite the thousands of women followed, the study lacked sufficient power to establish a significant reduction in mortality from endometrial cancer, and more precise estimates of risks of neoplasia and circulatory diseases are available from case-control studies.[5,6] This is especially true for particular groups of women, such as those who used oral contraceptives at young ages. Cohort studies also tend to lack extensive information about confounding factors, which probably underlie the observed higher mortality from violent and accidental causes—even in women who had stopped using the pill. The association between long term oral contraception and cervical cancer has often been presumed to reflect confounding by sexual behaviour, but recent work suggests that oral contraceptives might promote the activity of human papillomavirus infections.[7]

Clearly a definitive balance sheet on oral contraception and health should incorporate information from all types of study, looking at morbidity as well as mortality. The benefits of oral contraceptives include reductions in the incidence of menstrual problems (such as dysmenorrhoea and menorrhagia), iron deficiency anaemia, pelvic inflammatory disease, functional ovarian cysts, and benign breast disease.[8] But how would one compare the relief of dysmenorrhoea in 1000 women with the causation of a stroke in one? A further limitation of this approach for assessing oral contraceptives is that no value is placed on avoiding the grief of unwanted pregnancy: pregnancy is counted only as a possible cause of morbidity and death. The outstanding benefit of oral contraceptives is that they prevent unplanned pregnancy with such a high degree of effectiveness, convenience, and reversibility.

Even if we confine attention to medical benefits and risks, the balance will vary between different countries. Whereas the relative risks of various conditions in oral contraceptive users appear to be similar in developed and developing countries,[5,6] the absolute risks will depend on the underlying incidence of diseases. Maternal mortality is not mentioned in the present study: in places such as parts of rural Africa, where women may have a 1 in 15 lifetime risk of dying from pregnancy related causes,[9] the effectiveness of oral contraceptives in preventing pregnancy will be overwhelmingly important. Spacing pregnancies can also be expected to reduce mortality from other causes in such populations.

The balance is also different for specific groups of women. The Royal College of General Practitioners' study focused attention on cardiovascular risks in older users of oral contraceptives who smoke cigarettes.[10] Reviewing all the evidence suggests that women who do not smoke, who have their blood pressure checked, and who do not have hypertension have no increased risk of myocardial infarction and little increased risk of stroke when they use combined oral contraceptives.[6] The challenge is to maximise benefits and minimise risks by offering appropriate advice to women about oral contraception and about alternative methods of controlling their fertility.

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Recently there has been concern about inappropriate medical barriers to contraceptive use,[11] and the World Health Organisation has proposed medical eligibility criteria.[12] Measuring blood pressure before prescribing an oral contraceptive is sensible; ordering a battery of blood tests is not. Again the appropriate components of family planning care will depend on the setting. It is easy to emphasise the importance of regular cervical screening in countries with organised programmes, but this will not yet be possible in many developing countries—even though the risk of cervical cancer is generally greater. We have learnt much about the effects of oral contraception. While further work is required to answer some questions, there is now an even greater need for research into ways of applying existing knowledge to improve the family planning services available to women and their partners.

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Down's syndrome, cardiac anomalies, and nuchal translucency

Fetal heart failure might link nuchal translucency and Down's syndrome

Since the first report on the ability of nuchal translucency measurement to detect pregnancies affected by Down's syndrome by Nicolaides et al in 1994[1] over 20 studies have been published on the issue. Despite all these efforts, however, the exact performance of nuchal translucency measurement in detecting Down's syndrome is still unknown. Recent large studies in low risk populations have evaluated the performance of nuchal translucency measurement in detecting Down's syndrome, but the result of the nuchal translucency measurement had already been used in the risk assessment (by identifying cases of Down's syndrome that would never have reached term). In these studies fetuses affected by Down's syndrome which have an increased nuchal translucency are thus more likely to be detected than those affected fetuses with a normal nuchal translucency—and this may inflate the reported detection rate of nuchal translucency measurement.[2–4] Even the two largest studies reported detection rates as different as 72%[5] and 54%.[6] As a consequence, the choice between nuchal translucency measurement and serum screening for Down's syndrome remains subject to debate.[7 8]

The paper by Hyett et al in this week's issue reports on the association between nuchal translucency and major defects of the heart and the great arteries (p 81).[9] Among 29 154 chromosomally normal pregnancies 28 out of 50 cases with major cardiac defects were detected using the 95th percentile of nuchal translucency as a cut off point. These findings support the hypothesis that increased nuchal translucency may be due to failure of the fetal heart.[10 11] But what are the practical consequences of these findings?

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A nuchal translucency above the 95th percentile in a population in which the prevalence of cardiac anomalies is 1-2 per 1000 implies a probability of a cardiac anomaly of about 1.5 per 1000. Referral of women with nuchal translucency measurements above the 95th percentile to a fetal cardiology unit would imply that 5% of all pregnant women have to be subjected to specialist fetal echocardiography for a chance of 1 in 66 (28/1850) of finding a cardiac anomaly. It is important to realise that 13 of the 50 cardiac anomalies reported by Hyett et al were detected at postmortem examination after intrauterine death or termination of the pregnancy for non-cardiac defects. In these 13 cases the only clinical consequence is an increased risk of a cardiac anomaly in a future pregnancy. If we exclude them, 5% of all pregnant women would be subject to specialist fetal echocardiography for a chance of 1 in 123 (15/1850) of finding a cardiac anomaly. Increasing the cut off value of nuchal translucency to 3.5 mm would reduce the number of referrals to just over 1%, for a chance of having a cardiac anomaly of 1 in 17. This may be far more acceptable, although the sensitivity drops under 50%.

When assessing the value of nuchal translucency measurement in detecting cardiac anomalies it is important to realise that at present there is no obstetric intervention for fetuses with cardiac anomalies diagnosed antenatally, other then referring these women to a centre with cardiosurgical facilities for delivery or termination of pregnancy. Moreover, we need to be aware of the anxiety induced in parents by referring them for additional fetal echocardiography. After the detection of increased nuchal translucency in

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